RADIATION DOSE FRACTIONATION IN POSTMASTECTOMY BREAST RECONSTRUCTION: SYSTEMATIC REVIEW AND META-ANALYSIS WITH EMPHASIS ON COMPLICATIONS

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Introduction

- The safety of moderate • hypofractionation (HF) compared to conventional fractionation (CF) for postmastectomy radiotherapy (PMRT) after immediate breast reconstruction has not been clearly established.
- This review aimed to **compare** complication profiles between HF and CF in this clinical setting.

Methods

- A literature search was conducted in Embase, MEDLINE, and Cochrane CENTRAL up to January 10, 2025.
- Inclusion: Studies comparing HF (2.4–2.7 Gy/fraction) and CF (1.8–2.0 Gy/fraction) in women who underwent PMRT after immediate breast reconstruction.
- **Exclusion: Studies involving** intraoperative or partial breast irradiation, brachytherapy, hyperfractionation, accelerated fractionation.
- Evaluated Complications: major complications, reconstruction failure, infection, capsular contracture, fat necrosis, wound dehiscence, reoperation, and hematoma.
- Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were estimated using a randomeffects model.

Major complications а

F	CE			Odde ratio M.H						
vent/Total	Event/Total	Odds ratio, M-H, random (95% CI)	Weight (%)	random (95% CI)	Study or subgroup	HF Event/Tetal	CF	Odds ratio, M-H, random (95% CI)	Weight (%)	Odds ratio
19/1446	138/1418	4	100.0	0.83 (0.51-1.35)		Eventriotal	Eventriotal			random (96
3/229	25/228	-	35.7	1.11 (0.62-1.99)	All patients	3/78	5/84		100.0	0.64 (0.15-2
30	6/27		11.6	1.27 (0.38-4.29)	RCT	1/12	1/12		29.6	0.87 (0.03-2
)/199	19/201		24.1	1.07 (0.55-2.07)	Mutter et al. (2023)	0/1	1/1	«	10.3	0.11 (0.00-1
= 1. P = 0.81: 12:	= 0%			1.07 (0.00 2.07)	Zhang et al. (2024)	1/11	0/11		19.3	3.29 (0.12-8
					Test for Heterogeneity: $\tau^2 = 1.64$; $\chi^2 = 1.40$, Test for overall effect: $Z = 0.08$, $P = 0.93$	df = 1, P = 0.24; I ² =	29%			
1/1217	113/1190	\Leftrightarrow	64.3	0.68 (0.29-1.63)						
4/176	19/91		21.5	0.33 (0.16-0.69)	RCS					
6	18/64	F	6.3	1.28 (0.21-7.60)	Kim et al. (2021)	2/66	4/72		70.4	0.53 (0.09-3
5/1035	76/1035	H	36.5	0.99 (0.71-1.37)						
= 2, P = 0.03; l ²	= 72%				Test for Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.56$, df = 2, P = Test for overall effect: Z = 0.60, P = 0.55	0.46; l² = 0%	0.	01 0.1 1 10 100		
.09; I² = 51%	0.0	1 0,1 1 10 100								
F v 1 3 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	rent/Total 9/1446 /229 30 /199 1. P = 0.81; ² /1217 /1217 /176 5 /1035 2. P = 0.03; ²	CF rent/Total Event/Total 9/1446 138/1418 /229 25/228 30 6/27 /199 19/201 1, P = 0.81; I ² = 0% 113/1190 /1217 113/1190 /176 19/91 5 18/64 /1035 76/1035 2, P = 0.03; I ² = 72% 09; F = 51% 00	F CF Odds ratio, M-H, random (95% CI) 9/1446 138/1418 \checkmark 9/1446 138/1418 \checkmark /229 25/228 \checkmark 30 6/27 \checkmark /199 19/201 \checkmark 1. P = 0.81; I ² = 0% \checkmark \checkmark /1217 113/1190 \checkmark /176 19/91 \checkmark 5 18/64 \checkmark /1035 76/1035 \checkmark /2; P = 0.03; I ² = 72% $0,1$ 10 100	F CF Odds ratio, M-H, random (95% Cl) Weight (%) 9/1446 138/1418 100.0 /229 25/228 35.7 30 $6/27$ 11.6 /199 19/201 24.1 1, P = 0.81; I ² = 0% 64.3 /1217 113/1190 64.3 /176 19/91 21.5 5 18/64 6.3 /1035 76/1035 36.5 2, P = 0.03; I ² = 72% 0,1 100	Fertification CF Event/Total Odds ratio, M-H, random (95% CI) Weight (%) Odds ratio, M-H, random (95% CI) 9/1446 138/1418 100.0 0.83 (0.51-1.35) /229 25/228 35.7 1.11 (0.62-1.99) 30 6/27 11.6 1.27 (0.38-4.29) /199 19/201 4 1.07 (0.55-2.07) 1, P = 0.81; P = 0% 44.3 0.68 (0.29-1.63) /1217 113/1190 44.3 0.68 (0.29-1.63) /176 19/91 44.4 1.28 (0.21-7.60) 30 18/64 36.5 0.99 (0.71-1.37) /2. P = 0.03; P = 72% 91 100	CF Odds ratio, M-H, random (95% Cl) Weight (%) Odds ratio, M-H, random (95% Cl) Study or subgroup 9/1446 138/1418 100.0 0.83 (0.51-1.35) All patients /229 25/228 35.7 1.11 (0.62-1.99) All patients 300 6/27 11.6 1.27 (0.38-4.29) All patients /199 19/201 24.1 1.07 (0.55-2.07) Zhang et al. (2023) /1217 113/1190 64.3 0.68 (0.29-1.63) Zhang et al. (2024) /176 19/91 21.5 0.33 (0.16-0.69) RCS /1035 76/1035 63.3 1.28 (0.21-7.60) Kim et al. (2021) /1035 76/1035 36.5 0.99 (0.71-1.37) Test for Heterogeneity: r ² = 0.00; x ² = 1.56, df = 2. P = Test for overall effect: Z = 0.00; x ² = 1.56, df = 2. P = Test for overall effect: Z = 0.00; x ² = 1.56, df = 2. P = Test for overall effect: Z = 0.00; x ² = 1.56, df = 2. P = Test for overall effect: Z = 0.00; x ² = 1.56, df = 2. P = Test for overall effect: Z = 0.00; x ² = 1.56, df = 2. P = Test for overall effect: Z = 0.00; x ² = 1.56, df = 2. P = Test for overall effect: Z = 0.00; x ² = 1.56, df = 2. 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(2021) 2/66 4/72 /1035 76/1035 36.5 0.99 (0.71-1.37) Test for Heterogenety: r ² =0.00; P ² =0.55, df=2, P=0.46; P = 0% Test for overall effect: Z = 0.00; P = 0.55 0.0 /1035 0.1 10 100 100 100 0.0 100 0.0	CF prent/Total Odds ratio, M-H, random (95% CI) Weight (%) Odds ratio, M-H, random (95% CI) HF CF Event/Total Odds ratio, M-H, random (95% CI) 9/1446 138/1418 100.0 0.83 (0.51-1.35) 1.11 (0.62-1.99) Study or subgroup HF CF Odds ratio, M-H, random (95% CI) 300 6/27 11.6 1.27 (0.38-4.29) 11.6 1.27 (0.38-4.29) RCT 1/12 1/12 1/199 19/201 24.1 1.07 (0.55-2.07) Herogeneity, r ² = 1.84; x ² = 1.40, df = 1, P = 0.24; P = 20% Test for Heterogeneity, r ² = 1.84; x ² = 1.40, df = 1, P = 0.24; P = 20% Test for Heterogeneity, r ² = 1.60, gf = 1, P = 0.24; P = 20% Test for Heterogeneity, r ² = 0.00; x ⁴ = 1.56, df = 2, P = 0.46; P = 0% Odds ratio, M - H, random (95% CI) 1/127 113/1190 64.3 0.68 (0.29-1.63) RCS Test for Heterogeneity, r ² = 0.00; x ⁴ = 1.56, df = 2, P = 0.46; P = 0% Test for overall effect: Z = 0.00, P = 0.93 Test for Verse of the test overall effect: Z = 0.00; x ⁴ = 1.56, df = 2, P = 0.46; P = 0% Out Out Out I I I 1/103 76/1035 10 10 10 10 10 10 10 10 10 10 10 10 <td< td=""><td>CF ent/Total Odds ratio, M-H, random (95% Cl) Weight (%) Odds ratio, M-H, random (95% Cl) HF random (95% Cl) CF Event/Total Odds ratio, M-H, random (95% Cl) Weight (%) 9/1446 138/1418 100.0 0.83 (0.51-1.35) 11.11 (0.62-1.99) 11.6 1.27 (0.38-4.29) 35.7 1.11 (0.62-1.99) All patients 3/78 5/84 90.6 29.6 /199 19/201 1.0.7 (0.55-2.07) 11.6 1.27 (0.38-4.29) 0/1 1/1 0/1 29.6 /1176 19/91 64.3 0.68 (0.29-1.63) 0/1 1/11 0/11 11.9 19.3 1/105 76/1035 6.3 1.28 (0.21-7.60) 36.5 0.99 (0.71-1.37) 128 (0.21/1.60) Kim et al. 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b <u>Reconstruction fai</u>	lure					Study or subgroup	HF	CF	Odds ratio M-H random (95% CI)	Weight (%)	Odds ratio
Study or subgroup	HF	CF	Odds ratio M H random (95% CI)	Weight (%)	Odds ratio, M-H,	Study of subgroup	Event/Total	Event/Total	odus fallo, M-H, falldolli (55% cl)	weight (%)	random (S
Study of subgroup	Event/Total	Event/Total	Odus rado, M-H, randolii (#5% CI)	weight (%)	random (95% CI)	All patients	9/177	21/185		100.0	0.45 (0.15
All patients	14/96	16/94		100.0	1.34 (0.15-11.84)	RCT					
RCT with photon therapy						Zhang et al. (2024)	4/66	3/67		33.4	1.38 (0.30
Zhang et al. (2024)	9/66	15/67		60.3	0.55 (0.22-1.36)						
						RCS	5/111	18/118		66.6	0.27 (0.09
RCT with proton therapy						Chang et al. (2019)	0/50	3/25	e	11.7	0.06 (0.00
Mutter et al. (2023)	5/30	1/27		39.7	5.20 (0.57-47.69)	Song et al. (2020)	5/55	7/29		42.9	0.31 (0.09
						Barnes et al. (2024)	0/6	8/64		12.0	0.51 (0.03
Test for Heterogeneity: $x^2 = 1.84$, $y^2 = 3.46$, df = 1. D =	0.06:12 = 71%					Test for Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.14$,	df = 2, P = 0.57; I ² =	: 0%			
Test for overall effect: $Z = 0.26$, $P = 0.79$	0.00, 1 7 1 76	0.0	01 0.1 1 10 100			Test for overall effect: Z = 2.36, P = 0.02					
C Infection						Test for Heterogeneity: $r^2 = 0.32$; $\chi^2 = 4.00$, df = 3, P = Test for gueral effect: $Z = 1.42$, $P = 0.16$	0.26; 2 = 25%	0.	01 0.1 1 10 100		

meetion						rest for overall effect. 2 = 1.42, P = 0.10					
Study or subgroup	HF	CF	Odds ratio, M-H, random (95% Cl)	Weight (%)	Odds ratio, M-H,	g Reoperation					
	Event/Total	Event/Total			random (95% CI)	Study or subgroup	HF	CF	Odds ratio, M-H, random (95% CI)	Weight (%)	Odds ratio
All patients	23/295	21/295		100.0	1.15 (0.28-4.78)	etauj et eurgreup	Event/Total	Event/Total			rando m (9
RCT with photon therapy	15/265	21/268		83.5	0.71 (0.36-1.42)	All patients	10/125	22/155		100.0	0.74 (0.13-
Wong et al. (2024)	1 1/19 9	13/201		45.5	0.85 (0.37-1.94)	RCS with photon therapy	4/111	17/118		69.8	0.34 (0.11-
Zhang et al. (2024)	4/66	8/67	F	38.0	0.48 (0.14-1.66)	Chang et al. (2019)	0/50	2/25	e	17.3	0.09 (0.00-
Test for Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.57$, Test for overall effect: $Z = 0.97$, $P = 0.33$	df = 1, P = 0.45; l ² =	= 0%				Song et al. (2020)	3/55	5/29		29.4	0.28 (0.06-
·,·						Barnes et al. (2024)	1/6	10/64	· · · · · · · · · · · · · · · · · · ·	23.1	1.08 (0.11-
RCT with proton therapy						Test for Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.77$,	df = 2, P = 0.41; l ² =	0%	i I		
Mutter et al. (2023)	8/30	0/27		16.5	20.78 (1.14-379.92)	Test for overall effect: Z = 1.82, P = 0.07					
						RCS with proton therapy					
rest for Heterogeneity: τ² = 0.97; χ² = 5.99, df = 2, Ρ =	0.05; 2 = 67%					Smith et al. (2019)	6/14	5/37		30.2	4.80 (1.16-
Test for overall effect: Z = 0.20, P = 0.84		0.0	01 0.1 1 10 100								
d Capsular contractu	lre										
Study or subgroup	HF	CF	Odds ratio M H random (95% CI)	Weight (%)	Odds ratio, M-H,	Test for Heterogeneity: τ^2 = 2.11; χ^2 = 9.82, df = 3, P = Test for overall effect: Z = 0.33, P = 0.74	0.02; 2 = 69%	0.	01 0.1 1 10 100		

Study or subgroup	HF Event/Total	CF Event/Total	Odds ratio, M-H, rand		
All patients	94/850	114/763	<	>;	
RCT	17/84	26/82			
Mutter et al. (2023)	0/29	5/26	< =		
Zhang et al. (2025)	17/55	21/56	+		
Test for Heterogeneity: $r^2 = 1.87$; χ Test for overall effect: Z = 0.94, P	² = 2.54, df = 1, P = 0.11; l² = 0.35	= 61%			
RCS	77/766	88/681		-	
Chang et al. (2019)	4/50	8/25			
Kim et al. (2021)	0/101	3/19	~ =	-	
Ryu et al. (2024)	73/615	77/637		H	
Test for Heterogeneity: $r^2 = 1.90$; χ Test for overall effect: $Z = 1.49$, P	² = 11.32, df = 2, P = 0.003 = 0.14	, l² = 82%		1	
Fest for Heterogeneity: $\tau^2 = 0.66$; $\chi^2 = 14.28$ Fest for overall effect: Z = 1.98, P = 0.05	8, df = 4, P = 0.006; I² = 72%	c	0.01 0.1	1 10	
			Favors	HF Favors C	

Reference [1] Wong JS et al. Hypofractionated vs Conventionally Fractionated Postmastectomy Radiation After Implant-Based Reconstruction: A Randomized Clinical Trial. JAMA Oncol. 2024;

e Fat necrosis

95% CI)	Weight (%)	Odds ratio, M-H, random (95% CI)				
	100.0	0.38 (0.15-0.99)				
	36.8	0.34 (0.03-3.31)				
	8.1	0.07 (0.00-1.26)				
	28.7	0.75 (0.34-1.64)				
	63.2	0.25 (0.04-1.55)				
	21.2	0.18 (0.05-0.69)				
	7.9	0.02 (0.00-0.47)				
	34.1	0.98 (0.70-1.38)				
100						

T Wound dehiscence

h <u>Hematoma</u>

Study or subgroup	HF Event/Total	CF Event/Total	Odds ratio, M-H, random (95% CI)	Weight (%)	Odds ratio random (9
All patients	0/190	2/128		100.0	0.37 (0.04-3
Smith et al. (2019)	0/14	1/37		49.3	0.84 (0.03-2
Kim et al. (2021)	0/176	1/91		50.7	0.17 (0.01-4
Test for Heterogeneity: τ ² = 0.00; Test for overall effect: Z = 0.84, P	χ ² = 0.47, df = 1, P = = 0.40	0.50; l ² = 0%	.01 0.1 1 10 100		
			Favors HF Favors CF		

Figure 1. Forest plots of odds ratios comparing hypofractionation and conventional fraction (a) major complications, (b) reconstruction failure, (c) infection, (d) capsular contracture, (e necrosis, (f) wound dehiscence, (g) reoperation, and (h) hematoma.

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	Results
atio, M-H, n (95% CI) 15-2.75) 03-22.27)	 From 2,523 records, 11 studies (3,611 patients), including three RCTs, were selected.
12-89.81)	 Eight studies exclusively used photon beams.
09-3.00)	 Major complications were comparable between HF and CF (OR: 0.83, 95% CI: 0.51–1.35) (Figure 1).
ratio, M-H, n (95% CI) .15-1.35) .30-6.40)	 HF was associated with a significantly lower incidence of capsular contracture (OR: 0.38, 95% CI: 0.15–0.99) (Figure 1).
.09-0.80) .00-1.28) .09-1.10)	 No significant differences for other outcomes (Figure 1).
atio, M-H, n (95% CI)	 Patient-reported outcomes, assessed in Wong et al. [1], showed no significant difference in the physical well-being.
.13-4.25) .11-1.09)	
.00-2.02) .06-1.25) .11-10.25)	<u>Conclusion</u>
.16-19.80)	 HF is at least comparable to CF for the assessed complications.
tio, M-H, (95% Cl) 04-3.68) 03-21.81) 01-4.24)	 HF may reduce the risk of capsular contracture, suggesting its potential advantage in minimizing complications.
nation: e) fat	
10:1370-8.	Preprint available→